

Stanford NTROI Team Detailed Description:

A.1. Mission. The Stanford Team in the Network for Translational Research in Optical Imaging (NTROI) consists of five unique intellectual and technological environments that have themselves been supporting broad and multifaceted research programs on optical methods for the detection and study of malignancy. The Team brings the strengths of these individual sites together for an integrated Program dedicated to using innovative optical technologies to reveal the basic molecular mechanisms of oncogenesis and disease progression with the objective of advancing clinical detection and diagnosis.

A.2. Overview. Investigators in this program assembled to address the need to detect and localize neoplastic changes specifically in the esophagus. For this purpose we are developing miniaturized high-resolution dual axes confocal microscopes and new classes of fluorescence compounds for molecular characterization of disease. The goal is to better identify and classify lesions consisting of specialized intestinal metaplasia of the esophagus (Barrett's esophagus), low- and high-grade dysplasia, and esophageal adenocarcinoma with high sensitivity and specificity by combining fluorescence endoscopy for wide-area surveillance with confocal microscopy for sub-cellular detection. The optical contrast agent development work is targeting markers of neoplastic changes in the mucosa, such as cyclooxygenase-2 (*COX-2*) and cell surface markers. Instrument development includes design, fabrication, and validation of a miniature MEMS confocal microscope and modification of an existing fluorescence endoscopy system for infrared detection. We will clinically evaluate a system that combines high-resolution confocal imaging with wide area surveillance using reflectance for deep tissue penetration and fluorescence for contrast enhancement. Clinical results will be used to optimize the instrumentation and assess reagent efficacies.

The Stanford NTROI team is dedicated to the translation and validation of optical imaging modalities and chemistries. The team consists of investigators who will advance the reagents for molecular diagnosis of disease, design and build miniaturized microscopes using MEMS technology and design effective clinical trials to validate the proposed imaging strategies. This team of investigators has a record of effective collaborations. They are committed to developing interactive integrated processes of validation and design improvement. A key Team objective is phased development of miniaturized dual axes confocal instrumentation for combined structural and functional analyses of diseases of the esophageal mucosa. Our research findings will be immediately applicable to diseases of the esophagus, and we anticipate that they will find much wider application in the recognition of other premalignant conditions of the gastrointestinal tract, such as gastric premalignant states, colonic polyps (particularly flat and depressed lesions) or early colon cancer, or in the long-term management of inflammatory bowel disease. Furthermore, this approach may be relevant in general to the study of diseases that originate from the epithelial surface of any hollow organ.

A.2.1. Projects.

A.2.1.1. Project 1. Development of a miniaturized dual axes confocal microscope. The objectives of this Project are as follows: 1) miniaturize the dual axes confocal microscope design for the collection of reflectance images, first to a 5 mm and then to a 3.2 mm package diameter (developed by Core A); 2) characterize the performance of the dual axes confocal microscope *ex vivo* with reflectance images collected from normal and neoplastic mucosa of rabbit esophagus, 3) collect reflectance images with the dual axes confocal microscope *in vivo* from the rabbit model and compare with histopathology obtained by standard pinch biopsy, 4) collect reflectance images with the 5 mm diameter dual axes confocal microscope in human subjects with a history of Barrett's esophagus using a special therapeutic upper endoscope (Olympus XT30) that has a 6 mm diameter instrument channel and compare to standard histopathology, 5) collect reflectance

images with the 3.2 mm diameter dual axes confocal microscope using the LIFE II endoscopy system for wide area surveillance simultaneously and compare with standard histopathology. Investigators from Core A: Instrument Development and MEMS will work closely with investigators from Core B: Clinical Imaging and Pathology to develop the dual axes confocal microscope for clinical use, integrate the miniature dual axes confocal microscope with the LIFE II endoscopy system, collect confocal reflectance images in the rabbit model and in human subjects, and interpret all images for comparison with standard histopathology.

A.2.1.2. Project 2. Identification of novel targets of neoplasia in the esophagus. The objectives of this Project are as follows: 1) identify molecular markers of neoplasia in the esophagus using a phage display library to screen for small peptides that exhibit preferential binding to cell surface antigens in tumorigenic but not in non-tumorigenic cells in culture; 2) develop the use of cDNA microarrays to identify unique surface markers from neoplastic esophageal mucosa to validate the peptides selected by phage display and to identify additional surface markers, 3) modify the selected peptides with near-infrared (NIR) fluorescence dyes; 4) collect fluorescence images from NIR-labeled peptides bound to the esophageal mucosa of the Sprague-Dawley rat model of Barrett's esophagus *ex vivo* and *in vivo*; 5) collect confocal fluorescence images from the rat esophagus labeled with the peptide markers *ex vivo* and *in vivo* using the 3.2 mm diameter dual axes microscope (developed by Core A); 6) assess the rabbit and rat esophagus and necropsy specimens for local and systemic toxicity from applied NIR-labeled peptide markers; 7) collect fluorescence images with the LIFE II endoscopy system from human sprayed with NIR-labeled peptide markers followed by images with the miniature dual axes confocal microscope. Investigators from the Clinical Imaging Core will work closely with investigators from the Pathology Core to correlate the molecular markers selected by phage display library and cDNA microarrays with the stage of neoplastic transformation of the esophagus, to assess for potential toxicity of the NIR-labeled markers to animal models, and to correlate the endoscopic and confocal fluorescence images with histopathology.

A.2.1.3. Project 3. Cox-2 as a marker of neoplasia: novel optical imaging agents. The objectives of this Project are as follows: 1) Develop novel reagents that bind to the COX-2 receptor, a marker of disease progression that has already been evaluated and documented on neoplastic cells; 2) modify these reagents with NIR fluorescence dyes; 3) collect fluorescence images from NIR-labeled COX-2 markers bound to the esophageal mucosa of the Sprague-Dawley rat model of Barrett's esophagus *ex vivo* and *in vivo*; 4) collect confocal fluorescence images from the rat esophagus labeled with the COX-2 reagents *ex vivo* and *in vivo* using the 3.2 mm diameter dual axes microscope (developed by Core A); 5) assess the rat esophagus and necropsy specimens for local and systemic toxicity from applied NIR-labeled COX-2 markers; 6) collect fluorescence images with the LIFE II endoscopy system from human esophagus sprayed with NIR-labeled COX-2 markers followed by images with the miniature dual axes confocal microscope. Investigators from the Clinical Imaging Core will work closely with investigators from the Pathology Core to evaluate the level of COX-2 expression with the stage of neoplastic transformation of the esophagus by fluorescence imaging, to assess for potential toxicity of the NIR-labeled COX-2 markers to animal models, and to correlate the endoscopic and confocal fluorescence images with histopathology.

A.2.1.4. Core A. Instrumentation Development and MEMS Core. Core A has been designed to develop the instrumentation for collecting reflectance and fluorescence images from animal and human esophageal mucosal in Projects 1, 2, and 3. The instrument platforms include the breadboard dual axes confocal prototype, miniature dual axes confocal prototype at $\lambda = 1345$ nm and $\lambda = 750$ nm, and the LIFE II endoscopy system for wide area surveillance. In Project 1, reflectance imaging at $\lambda = 1345$ nm will be used to evaluate the morphological features of normal and neoplastic esophageal mucosa with deep tissue penetration using an uniaxial scan mirror and

a pneumatic piston to perform vertical cross-sectional imaging. In Projects 2 and 3, reflectance and fluorescence images will be collected simultaneously from esophageal mucosa and NIR-labeled molecular markers, respectively, using biaxial scan mirrors to perform horizontal cross-sectional imaging. Fluorescence detection of the NIR-labeled markers developed in projects 2 and 3 will first be developed with the breadboard dual axes prototype. In addition to optimizing the optics and the response and bandwidth of the detector, a novel frequency modulation scheme using a high NA collection optic will be developed to significantly improve the fluorescence collection efficiency. Other support services of this core include 1) the design and implementation of electronic control circuitry; 2) the development of imaging acquisition, processing, and display software, and 3) optical modeling methods for introducing improvements and modifications determined by preliminary clinical experience. This core includes investigators from our industrial collaborator, Optical Biopsy Technology, Inc (OBTI), who will facilitate the rapid transition of successful developments in imaging instrumentation to the commercial setting for mass production and broad distribution. This imaging technology can then be available for other clinical settings at an affordable cost.

A.2.1.5. Core B. Clinical Imaging and Pathology Core. Core B has been designed to develop methods and procedures for testing and validating the optical imaging instruments developed in Core A for the study of animal models and human subjects in Projects 1, 2, and 3. While the investigators are separated into either the Clinical Core or Pathology Core for logistical reasons, we have integrated these two groups in this Core to streamline the evaluation and validation of novel technologies. In Project 1, we will collect reflectance images at $\lambda = 1345$ nm to evaluate the morphological features of normal and neoplastic esophageal mucosa first in the rabbit model *ex vivo* and then *in vivo*. These experiments will provide valuable information regarding the imaging requirements needed to successfully collect images *in vivo* with the miniature dual axes confocal microscope, and the results will likely be used to assist Core A in modifying the instrument design in an iterative fashion. Once the miniature dual axes microscope is validated in animal models, the investigators in Core A will use it to collect reflectance images in human subjects during routine endoscopy. The Core A investigators will be involved in all aspects of the clinical imaging project, including submitting IRB protocols, recruitment of human subjects, obtaining informed consent, doing routine endoscopy, performing LIFE II endoscopy for wide area surveillance, collecting confocal images with the dual axes instrument, obtaining standard pinch biopsy, and correlating the confocal images with histopathology. In Projects 2 and 3, the members of Core A will investigate the application of NIR-labeled fluorescence markers consisting of small peptides and COX-2 reagents to the Sprague-Dawley rat model of Barrett's esophagus. The Clinical Imaging Core will be responsible for collecting, storing, and processing reflectance and fluorescence images from the esophageal mucosa. The Pathology Core will be responsible for assessing the esophageal and necropsy specimens for local and systemic toxicity associated with application of the NIR-labeled markers. Once the dyes are determined to be safe for human use when administered by mucosal spraying, the Clinical Core investigators will perform the same imaging tasks for human subjects as described above for reflectance imaging. In addition, they will perform baseline tests to monitor for toxicity associated with the NIR-labeled dyes, including blood tests, electrocardiograms, and urine analyses. Furthermore, the Clinical Core investigators will follow up with the human subjects via telephone to monitor for the onset of new symptoms that may develop from dye application.

A.2.1.6. Core C. Administrative Core. This core is comprised of lead investigators at all of the sites in this program, including: Christopher Contag, Gordon Kino, Olav Solgaard, David Piston, George Triadafilopoulos, Michael Mandella, and Jim Crawford.

A.2.1.7. Development Projects.

A development fund will be established to support projects that lack the preliminary data for an R01 level application with the intent of seeding innovative projects that will advance and complement the existing program. The topics and selection criteria for additional projects are listed below. The review criteria for each of the development projects include scientific excellence, relevance to revealing the molecular basis of malignancy and disease progression using *in vivo* analyses, and innovation.

The selection of two-year development projects will begin in year 2. Selection of these projects will include consideration of how the project will increase the breadth and capability of our Network to either extend our technologies and compounds to other diseases or advance the technologies and strategies for the detection and characterization of premalignant metaplastic lesions and early esophageal cancer. Upon notification of U54 funding, an RFA will be released to faculty at all of the sites in this program and to other Network participants requesting applications for new development projects that relate to *in vivo* confocal microscopy and reagent development. Applications will be solicited for grants that complement the cancer-related and imaging research themes of this Network Program. We will work with the site directors, as part of the executive committee, to encourage development within the program by engaging faculty who are associated with the Network to think broadly about the problem of *in vivo* diagnosis through advancing technologies that assess molecular markers of disease and utilize *in vivo* histopathology. We will seek associate members who are working in related fields and encourage their participation in this program. The topics that will be highlighted in this development fund will include, but are not be limited to the following topics:

- Biochemical markers of metaplasia, oncogenesis and disease progression
- Understanding gene function in epithelial disease
- Development of optically-based imaging compounds
- Molecular therapeutics
- Novel therapeutic targets
- Nucleic acid-based therapies for epithelial disease
- Immune surveillance and immune cell therapies of neoplasia
- *In vivo* detectable disease markers
- Signals for disease progression
- New optical methods of disease detection
- Advances in multimodality imaging approaches
- Technologies for *in vivo* molecular characterization of disease
- Use of dual axes confocal technologies for disease detection
- Clinical uses of dual axes confocal technologies
- Two photon imaging methods

The Executive committee will review the submitted applications and recommend two new projects for funding every two years, beginning in year 2, with a funding duration of 2 years at \$150k/year. The review committee will be flexible as to accommodate the funding of more than two projects in each review period if highly innovative, but risky, projects are proposed that require “seed funds” and shorter funding periods. Descriptions of the development projects that are recommended for funding will be forwarded to the NTROI Steering Committee for review.

A.2.2. Scientific and Technological Areas.

Although the team and the research projects in this Network are multidisciplinary in nature, the investigators can be grouped into five thematic areas including; Engineering Biology, Biochemistry, Clinical Imaging and Pathology. The Program is organized in a multidimensional

format that is best represented in this thematic structure involving investigators at the various sites. The interactive nature of this proposal is demonstrated by marking (**in bold**) the investigators in each thematic area highlighting the involvement of investigators from different sites and with different expertise in each area. For an integrated program in translational medicine it is necessary to have broadly trained individuals who can link the various thematic areas. Each member of the team is broadly trained and is listed in several of the thematic areas. This will greatly enhance the development of clinical imaging instrumentation and reagents as the input from the clinical studies will feed directly into the design and improvement of the tools. Here we describe each of these thematic areas and their role in the Network as well as the investigators expertise and roles in each area.

A.2.2.1. Engineering. The instrumentation design that forms the basis for this Network, the dual axes confocal microscope, was initially described by the research team lead by **Dr. Gordon S. Kino**; he is a Co-Principal Investigator of this NTROI Team. He and Timothy Corle are the authors of *Confocal Optical Microscopy and Related Techniques*, Academic Press (1996) and is the original developer of the miniaturized confocal microscope using MEMS fabrication techniques. His research interests include high-frequency fiber optic devices, scanning optical and acoustic microscopes, fiber optic sensors, and applications of micromachining techniques to microscopy. **Dr. Kino's** research combines physical optics, and digital signal processing. **Dr. Kino** will lead the engineering efforts of the Team and will participate in the design and development of the MEMS dual axes microscopes that lie at the heart of this proposal.

Dr. Kino will work closely with **Drs. Olav Solgaard** and **Michael Mandella** who are PI's on **Project 1 and Core A**, the engineering-oriented projects. The objectives of these two components of the Network are to design and build the miniaturized dual axes confocal microscopes. This will be accomplished in two phases. In the first phase a 5mm reflectance imaging microscope that operates in the near infrared (nir) will be designed and built from commercially available materials. **Dr. Mandella**, the Chief Technology Officer of OBTI, will lead this project, which is described in Core A, and will work closely with **Drs. Solgaard** and **Kino**. **Dr. Mandella** is an expert in the design and development of optical instrumentation for confocal microscopy and optical coherence tomography, and has constructed and packaged numerous optical instruments designed for eventual miniaturization for use as high speed, catheter based imaging systems.

The second phase of the microscope development is to further miniaturize the system and add capability for fluorescence imaging, and will be lead by **Dr. Solgaard**, Assistant Professor of Electrical Engineering at Stanford University. His expertise is in the area of micro-electro-mechanical systems (MEMS) mirrors, scanners and phased arrays for high-speed, high-resolution imaging, and his background is ideally suited for the design and development of this next phase, which is described in **Project 1**. **Dr. Solgaard**, along with **Drs. Kino** and **Mandella**, will design the uniaxial and biaxial MEMS scanning mirrors for vertical and horizontal scanning, and direct the fabrication, assembly, and testing of the miniature dual-axes confocal microscope. **Dr. Solgaard's** interests are in biomedical applications of MEMS technology and he will work at the interface between the clinical applications and engineering, along with **Drs. Triadafilopoulos** and **Wang** to optimize the instrumentation designs for clinical applications.

Dr. Sam Wells complements the engineering component with research interests in multi-spectral and intra-vital imaging, he will use his expertise for the spectroscopic and quantitative microscopic characterizations of the COX-2 imaging agents. He is a Research Associate Professor in Molecular Physiology and Biophysics at Vanderbilt University, is the Managing Director of the Cell Imaging Resource, and is an expert in fluorescence imaging. **Dr. Well's** expertise ties this thematic area to the biochemistry and biology as a link between optical instrumentation and reporters.

A.2.2.2. Biology. This thematic group's efforts will be directed at novel markers of esophageal disease and animal models. Much of the work in this thematic area will be performed in **Project 2** in the identification of novel markers by microarray analyses and screening of peptides libraries. This project will be led by **Dr. Contag**, an Assistant Professor in the Departments of Pediatrics, Radiology and Microbiology & Immunology, and an active faculty member in the Multidisciplinary Programs in Immunology, Molecular Imaging and Biomedical Engineering. In Project 2 one aim is to identify novel molecular targets of neoplasia in the esophagus, including intestinal metaplasia (Barrett's esophagus), dysplasia, and adenocarcinoma, using peptide ligands that bind to cell surface antigens. Toward this end, a phage display library with a complexity of 10^{11} unique peptides will be screened. These peptides contain 9 to 12 amino acids, and have several advantages over antibodies for binding to markers of neoplasia. The cell culture assays will be shared among the sites and include a Barrett's adenocarcinoma-derived cell line (TE7) as a model of neoplasia, and an esophageal cell line (HET-1A) as a model of non-tumorigenic tissue. The peptides will be labeled with the same infrared dyes as the Cox-2 inhibitors (e.g. indocyanine green, Cy 7, and Alexa Fluor 750). While cell lines are convenient *in vitro* models for identifying candidate peptides, we will also evaluate resected specimens of esophageal mucosa from human subjects with selected peptides using cDNA microarrays. **Dr.**

Triadafilopoulos and members of his laboratory will use microarrays to identify unique cell surface or intracellular molecular changes that occur in the early stages of metaplastic transformation. The arrays will be used to validate the peptide library screens, identify additional surface markers that can be used for screening peptides, and reveal unique intracellular pathways that can be targeted in addition to Cox-2 markers. As part of the clinical imaging and pathology Core, optical imaging of the peptide-dye conjugates and COX-2 inhibitors will then be performed first with wide area surveillance using the LIFE II endoscopic imaging system (Xillix Inc.) and then with sub-cellular evaluation with a MEMS dual axes confocal microscope. Interpretation of results will be aided by the expertise of **Drs. Crawford** and **Campbell-Thompson** of **Core B**.

Dr. Jonathan W. Hardy, a Research Associate in the Contag Lab, will take the lead in screening of phage display libraries and the characterization of phage with regard to binding specificity and sequence. He will work with **Dr. Wang** and the Vanderbilt team (**Drs. Piston and Marnett**) to optimize the incorporation of fluorescent tags into the selected peptides for development as probes. **Drs. Hardy** and **Wang** will conduct the pre-clinical studies of the peptide-based probes as directed by **Drs. Crawford** and **Triadafilopoulos**.

A.2.2.3. Biochemistry. **Dr. Larry Marnett** leads the biochemistry thematic area. His research focuses on the biochemistry and molecular biology of oxidation of natural and synthetic chemicals, and here he will investigate the mechanisms of oxidation of arachidonic acid by cyclooxygenase and lipoxygenase enzymes and their inhibition by non-steroidal anti-inflammatory drugs. From this he will work with **Dr. Dave Piston** in the design, synthesis, and biochemical evaluation of selective cyclooxygenase-2 (COX-2) inhibitors and fluorescent dyes to develop markers for cell transformation. **Dr. Piston's** research interests include basic molecular mechanisms involved in glucose metabolism and insulin secretion in β cells within intact functioning pancreatic islets. He will work with **Dr. Marnett** on the synthesis of COX-2 inhibitor ligands. **Dr. Piston** is the Principal Investigator of the Vanderbilt Component of this Network and of **Project 3**. The Biochemistry team will work closely with **Drs. Contag, Kino** and **Triadafilopoulos**, and the other members of the Network to optimize the use fluorescent Cox-2 inhibitors in pre-clinical models and clinical applications, and to link reagent development to the technology of dual axes confocal microscopes—integrated reagent and hardware development.

As part of this Network, **Dr. Marnett** will supervise the design and execution of all the chemical preparations and will work closely with **Drs. Piston** and **Triadafilopoulos** in overseeing the optical work in cell culture, animals, and clinical studies. **Drs. Marnett** and **Piston** have been

working together on many projects at the Cancer Network and *In Vivo* Cellular and Molecular Imaging Network at Vanderbilt over the last ten years. Both **Dr. Piston** and **Dr. Marnett** will interact closely with the leadership at the other sites and with **Drs. Contag** and **Hardy** on the development of fluorescently tagged peptides.

Dr. Carol Rouzer is a Research Professor in the Department of Biochemistry at Vanderbilt University and has the primary responsibility for all cell-based experiments with COX-2 imaging agents at the Vanderbilt site. She will work with **Drs. Wang** and **Hardy** on cell culture assays and she will be the primary contact for experimental interactions throughout the Network with the COX-2 imaging agents.

A.2.2.4. Clinical Imaging. The director of this thematic area is **Dr. George Triadafilopoulos**, and he serves as the PI of the Clinical Imaging and Pathology Core (**Core B**). His research interests concern factors involved in the pathogenesis of gastroesophageal acid reflux disease and Barrett's esophagus, and has ongoing studies in the area of Barrett's metaplasia. As PI of this Core, he will direct the collection of reflectance and fluorescence images during endoscopy, the design the clinical experiments for correlating the confocal images with pathology, and evaluate the interpretation of results. **Dr. Shai Friedland** is Board-Certified in Internal Medicine and Gastroenterology and is an Assistant Professor of Medicine at the Stanford University School of Medicine and a Staff Physician at the VA Palo Alto. He has 4 years of experience in clinical endoscopy and in clinical research methods for the development of new endoscopic technologies. As a link to the pathology group at University of Florida, he will perform the collection of reflectance and fluorescence images during endoscopy, participate in the design the clinical experiments for correlating the confocal images with pathology, and evaluate the interpretation of results along with **Dr. Roy Soetikno**. **Dr. Soetikno** will serve as Clinical Imaging Core Associate Director. Dr. Soetikno is Board-Certified in Internal Medicine and Gastroenterology by the ABIM. He is an Assistant Professor of Medicine at the Stanford University School of Medicine and the Chief of Endoscopy at the VA Palo Alto Health Care System. He will also participate in the collection of reflectance and fluorescence images during endoscopy, the design of the clinical experiments for correlating the confocal images with pathology, and evaluation and interpretation of results.

Dr. Jacques Van Dam is a Clinical Investigator on this project. He is Board-Certified in Internal Medicine and Gastroenterology by the ABIM. He is Professor of Medicine at Stanford University School of Medicine and is the Clinical Chief of Gastroenterology and Director of Endoscopy at Stanford. He also directs the Stanford program in interventional endoscopy (ERCP and EUS), and performs a large number of upper endoscopies, colonoscopic polypectomies and screening examinations for colorectal cancer. His involvement in this program includes performing and supervising the endoscopic procedures for collection of biopsy specimens in the gastrointestinal tract, obtaining data with novel optical imaging instruments, providing input for the design of clinical experiments, and assisting in the interpretation of results. He will perform the collection of reflectance and fluorescence images during endoscopy, design clinical experiments for correlating the confocal images with pathology, and evaluate the interpretation of results.

Dr. Thomas D. Wang is broadly trained in engineering, biology and medicine and will facilitate integration among the various thematic areas. Dr. Wang is Board-Certified in Internal Medicine by the ABIM. He is a biophysicist and optical engineer by training. He will be involved in many aspects of this project including contribution to the design and development of the MEMS dual axes prototype microscope, validating the imaging performance of the miniature prototype microscope, and collection of fluorescence images on excised tissues and *in vivo*. He will work with **Drs. Triadafilopoulos, Soetikno, and Van Dam** in the collection of the reflectance and fluorescence images during endoscopy, participate in design of clinical experiments for correlating confocal images with pathology, and evaluate the interpretation of results.

A.2.2.5. Pathology. **James M. Crawford, M.D., Ph.D.** will serve as the Director of the Pathology aspect of **Core B** by providing expert morphological assessment of Barrett's esophagus, dysplasia, the degree to which marker genes are expressed, immunohistochemistry of proteins, and the toxicology of the detection technologies and chemical interventions. **Dr. Crawford** is a world-expert in pathology of the gut and hepatobiliary tree. A primary focus for this work has been in rodent toxicology and inflammatory disease. **Dr. Crawford** is currently Core Pathologist for NIH-funded studies emanating from the Dana Farber Cancer Institute and University of Michigan Bone Marrow Transplant Program, in addition to funded research being conducted at the University of Florida. **Dr. Martha Campbell-Thompson** will serve as Pathology Core Associate Director. She brings experience in cellular immunolocalization of protein and mRNA for various gene families, including neuroendocrine hormones, growth factor and steroid hormone receptors, and others, in the gastrointestinal tract, central nervous system, and reproductive organs. Studies included morphometric analysis using videomicroscopy of intestinal dysplasia in a rat model of gastric carcinogenesis. She will perform initial screening of all samples for histopathology and coordinate reviews of histopathologic specimens with **Drs. Crawford** and **Detrisac**. **Dr. Campbell-Thompson** has experience in developing and managing web-based master databases and will thus be responsible for managing the histopathological review information generated with **Drs. Crawford** and **Detrisac**. She will communicate the summary reports to all of the project investigators. **Dr. Carol Destrisac** is a Board-Certified Anatomic Pathologist at the University of Florida College of Veterinary Medicine, and brings enormous expertise in morphological analysis of murine tissues. She will also provide expert consultative assessment of histopathology in rabbit and primate organs.